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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/010,725	11/30/2001	Wely B. Floriano	06618-607002	4307

7590 10/13/2004
SCOTT HARRIS
Fish & Richardson P.C.
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San Diego, CA 92122

EXAMINER

LY, CHEYNE D

ART UNIT	PAPER NUMBER
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1631

DATE MAILED: 10/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/010,725

Applicant(s)

FLORIANO ET AL.

Examiner

Cheyne D Ly

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 August 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-6 and 8-45 is/are pending in the application.
- 4a) Of the above claim(s) 17-28, 30 and 32-35 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8-16, 29, 31 and 36-45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 1-6 and 8-45 are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 6/04/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

1. Applicants' arguments filed August 09, 2004 have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.
2. The cancellation of claim 7, withdrawal of claims 17-28, 30, and 32-35, and addition of new claims 36-45 have been acknowledged.
3. Claims 1-6, 8-16, 29, 31, and 36-45 are examined on the merits.

CLAIM REJECTIONS - 35 U.S.C. § 112, FIRST PARAGRAPH

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-6, 8-16, 29, 31, and 36-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. NEW MATTER REJECTION.
6. The instant rejection has been necessitated by Applicant amendments.
7. Claim 1, lines 7-9, the limitation of "the preferred binding conformations...using docking techniques" has not been found in the specification. Further, Applicant's pointed to support in Applicant's argument (Remarks §, page 11, last paragraph) does not provide written basis

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support for the limitation of “generating and ranking initial conformations.” It is noted that the instant specification [0072] discloses “Ranking ligand affinities...”; however, said disclosure is different from the required limitation recited in lines 7-9 of claim 1. The same issue is present in claim 31, lines 8-10; claim 44 and 45 as directed to the limitation of “generating and ranking initial conformations.” Claims 2-6, 8-16, 29, 31, and 36-43 are rejected for being dependent from claim 1 or 31.

8. Claim 4, lines 8 and 10-11, the limitations of “scoring a preliminary energy function for at least some of the initial conformations” and “based at least in part on the preliminary energy scores” have not been found in the pointed to support in the instant specification.

9. Claim 5, lines 4-7, the limitation of “scoring a second preliminary energy function for each of the best conformations...the lowest second preliminary energy scores” have not been found in the pointed to support in the instant specification.

10. Claim 6, lines 2 and 5, the limitation of “preliminary energy function” has not been found in the pointed to support in the instant specification.

11. Claim 36, lines 6-7, the limitation of “scoring a preliminary energy function for at least some of the initial conformations” has not been found in the instant specification.

CLAIM REJECTIONS - 35 USC § 101

12. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

13. Claims 1-6, 8-16, 29, 31, and 36-45 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory algorithm type subject matter.

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14. This rejection is maintained with respect to claims 1-6, 8-16, 29, and 31 as recited in the previous office action mailed October 15, 2003.

15. The instant rejection, as necessitated by claim amendments, has been extended to new claims 36-45.

RESPONSE TO ARGUMENT

16. Applicant argues that independent claims 1 and 31 “output[] selected calculated binding energies...set of ligands”; therefore, the claimed method produces a useful, concrete, and tangible result. Applicant’s argument has been fully considered and found to be unpersuasive because the claimed invention is directed to a computer implemented method comprising steps for manipulating ligand-protein binding data without any physical alteration step, which is considered to be non-statutory subject matter. “For example, a computer process that simply calculates a mathematical algorithm that models noise is nonstatutory. However, a claimed process for digitally filtering noise employing the mathematical algorithm is statutory.” (MPEP § 2106 (IV)(B)(2) (b), part ii). Similar to the nonstatutory example above, the instant invention comprises algorithmic steps for manipulating ligand-protein binding data without any physical alteration resulted from said analysis or modeling steps. It is noted that claim 1, lines 15-17, and claim 31, lines 16-18, recite the limitation of “output the selected calculated binding energies.” However, said limitation could reasonably be construed as the exchange of electrical signal from one processor to another within a computer system. Therefore, said limitation does not cause any physical alteration resulted from said “output” step.

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17. It is acknowledged that the instant invention is directed to a computer program product on a computer-readable medium comprising means for manipulating ligand-protein binding data without any physical alteration step. However, "such activity is not determinative of whether the process is statutory because such transformation alone does not distinguish a statutory computer process from a nonstatutory computer process" (MPEP § 2106 (IV)(B)(2) (b), part ii).

Claim Rejections - 35 USC § 102

18. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

19. Claims 1-6, 8-16, 29, 31, and 36-45 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by Zou et al. (1999).

20. This rejection is maintained with respect to claims 1-6, 8-16, 29, and 31 as recited in the previous office action mailed October 15, 2003.

21. The instant rejection, as necessitated by claim amendments, has been extended to new claims 36-45.

RESPONSE TO ARGUMENTS

22. Applicant argues that the claimed invention is directed to provide a "hierarchical method for modeling ligand binding interactions" while Zou et al. "used a single model to rank ligands or conformations." Applicant's argument has been fully considered and responded to

below with cited disclosure by Zou et al. The newly cited disclosure has been necessitated by Applicant's claim amendments.

23. Further, Applicant argues that the methods of Zou et al. are "computationally demanding" while the claimed invention uses "efficient course-grained methods to first model initial conformations of ligands and identify preferred binding conformations..."

Applicant's arguments have been fully considered and found to be unpersuasive. The method of Zou et al. is to "improve the computational speed" for modeling ligand receptor binding interactions (Abstract etc.). Because the Office does not have the facilities for examining and comparing the applicant's claimed invention with the disclosure of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See *in re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

REJECTION RE-ITERATED

24. Zou et al. discloses a method and computer program for modeling ligand receptor binding interactions wherein structural information based on solvation effects for said receptors are derived from crystal structures to identify binding regions (page 8037, columns 1-2, III. Results, § 1). Zou et al. discloses "we first use DOCK to identify 10,000 top force field scoring molecules from the ACD and then carry out the GB calculations to rank these candidates... We also tested the capability our free energy scoring function to select the right conformations of a binding ligand out of a variety of possible conformations" (page 8037, column 2, Rank Ordering of Binding Affinities §). A 10 best scoring results (output)

according to free energy calculations for a plurality of conformations are disclosed in Table

4. The binding energy calculations are optimized in order to rank inhibitors correctly (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claims 1, 29, 31, and 36.

25. The crystal structures used for identifying binding regions are derived from dhfr-MTX (page 8037, columns 2, lines 3-5), as in instant claim 2.

26. The step of optimization for the parameter set is directed to known and unknown binding regions for predicting binding energies (page 8037, column 1, § 6. Optimization for the Parameter Set), as in instant claim 3.

27. Zou et al. discloses the treatment of solvent molecules in molecular dynamics simulations (page 8033, column 2, lines 14-15), unoccupied embedded space between ligand and the receptor (empty volume) is penalized in the said method (Abstract etc.), and energy minimization is performed with DOCK force field. "For comparison, we also score these ligand molecules based on the grid spacing of 0.3 Å (first energy function) and distance cutoff of 10Å (second energy function). Orientation minimization is performed and the results are given in Table 1 (page 8037, column 2, lines 1-19 and Table 1), as in instant claims 4-6, 8, 9, and 37.

28. Zou et al. discloses a simple solvation model uses atom or group-based solvent exposed area terms; and an approach wherein the solvent is treated as a continuum dielectric medium (page 8034, column 1, lines 12-13), as in instant claims 10, 11, 38, and 39.

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29. The binding energy for each ligand is calculated by taking the difference in the ligand energy of ligand in solvent and in receptor (page 8035, columns 2, § 3 and § 4 to page 8036, column 1), as in instant claims 12 and 40.

30. The method of Zou et al. is directed to globular protein and the calculation of dielectric constant of said protein in water (page 9035, column 1, lines 3-12), as in instant claims 13-16 and 41-43.

31. The method of Zou et al. above is relies on the general GB/SA model to compute ligand binding energies wherein the parameters a approximated by a linear dependence on the solvent-accessible surface area and dielectric properties around the binding site as directed to the unoccupied embedded space (page 8034, II. Method §, column 2, to page 8035, column 1, line 26). Using the method of Zou et al., the first set of parameters yields the best fit binding energies six inhibitors (subset). TMP and MTX rank no. 1 and no. 2 among top scoring 10,000 ACD molecules for dhfr (page 8040, column 1, lines 10-19), as in instant claims 44 and 45.

CONCLUSION

32. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

33. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory

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period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

34. This application contains claims 17-28, 30, and 32-35 drawn to an invention nonelected without traverse, filed July 28, 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

35. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

36. Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and

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history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

37. For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

38. Any inquiry concerning this communication or earlier communications from the examiner should be directed to C. Dune Ly, whose telephone number is (571) 272-0716. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

39. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (571) 272-0722.

C. Dune Ly
10/4/04

Andin H. Manschel 10/12/04
ANDIN H. MANSCHER
COMMUNITY COLLEGE

U.S. Patent and Trademark Office Information Disclosure Statement by Applicant (Use several sheets if necessary) (37, CFR § 1.98(b))	U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 06618-607002	Application No. 10/010,725
	Applicant Wely B. Floriano, Nagarajan Vaidehi, William A. Goddard, III		
	Filing Date November 30, 2001	Group Art Unit 1643 1631	

U.S. Patent Documents

Examiner Initial	Desig. ID	Patent Number	Issue Date	Patentee	Class	Subclass	Filing Date If Appropriate
CDL	AA	5,680,319	10/21/97	Rose et al.	364	496	
	AB	5,705,335	1/6/98	Hendry	435	6	
	AC	5,873,052	2/16/99	Sharaf	702	20	
	AD	5,854,992	12/29/98	Shakhnovich et al.	702	27	
	AE	5,940,307	8/17/99	Fischbarg et al.	364	496	

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation
	AF						Yes No

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
CDL	AG	D'Aquino, J. et al., "The Magnitude of the Backbone Conformational Entropy Change in Protein Folding," <u>Proteins: Structure, Function and Genetics</u> (1996) 25:143-156
	AH	Buck, L. et al., "A Novel Multigene Family May Encode Odorant Receptors: A Molecular Basis for Odor Recognition," <u>Cell</u> (1991) 65:175-187
	AI	Burkhard, P. et al., "An Example of a Protein Ligand Found by Database Mining: Description of the Docking Method and Its Verification by a 2.3 Å X-ray Structure of a Thrombin-Ligand Complex," <u>J. Mol. Biol.</u> (1998) 277:449-466
	AJ	Connolly, M.L., "Solvent-Accessible Surfaces of Proteins and nucleic Acids," <u>Science</u> (1983) 221(4612):709-713
	AK	Ding, H. Q. et al., "Atomic Level Simulations on a Million Particles: The Cell Multipole Method for Coulomb and London Nonbond Interactions", <u>J. Chem. Phys.</u> (1992) 97(6):4309-4315
	AL	Datta, D. et al, "Mechanism for Antibody Catalysis of the Oxidation of Water by Singlet Dioxygen" <u>PNAS</u> (2002) 99(5):2636-2641
	AM	Ding, H.Q. et al. "The Reduced Cell Multipole Method for Coulomb Interactions in Periodic Systems with Million-Atom Unit Cells", <u>Chem. Phys. Lett.</u> (1992) 196 (1,2):6-10
	AN	Dombi, G. et al., "Analysis of Protein Transmembrane Helical Regions by a Neural Network", <u>Protein Science</u> (1994) 3:557-566
	AO	Donnelly, D. "Modeling alpha-helical Transmembrane Domains", <u>Biochem. Society Transactions</u> (1993) 21:36-39
	AP	Ewing, T.A. et al., "Critical Evaluation of Search Algorithms for Automated Molecular Docking and Database Screening", <u>J. Comput. Chem.</u> (1997) 18:1175-1189
	AQ	Floriano, W. B. et al., "Molecular mechanisms underlying differential odor responses of a mouse olfactory receptor", <u>PNAS</u> (2002) 97(20):10712-10716
	AR	Gasteiger, J. et al., "Iterative Partial Equalization of Orbital Electronegativity - a Rapid Access to Atomic Charges", <u>Tetrahedron</u> (1980) 36:3219-3288

Examiner Signature

Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449
(Modified)U.S. Department of Commerce
Patent and Trademark OfficeAttorney's Docket No.
06618-607002Application No.
10/010,725Information Disclosure Statement
by Applicant

(Use several sheets if necessary)

Applicant

Wely B. Floriano, Nagarajan Vaidehi, William A. Goddard, III

Filing Date

November 30, 2001

Group Art Unit

~~1645~~ 631

(37 CFR 1.98(b))

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
CDL	AS	Ghosh, A. et al., "Generalized born model based on a surface integral formulation", <i>J. Phys. Chem.</i> (1998) 102:10983-10990
	AT	Guner, O., <i>Pharmacophore - Perception, Development and Use in Drug Design</i> (2000) 1-12
	AU	Huang, E. et al., "Ab Initio Fold Prediction of Small Helical Proteins Using Distance Geometry and Knowledge-Based Scoring Functions", <i>Journal of Molecular Biology</i> (1999) 290:267-281
	AV	Jain, A., et al., "A fast recursive algorithm for molecular-dynamics simulation", <i>J. Comp. Phys.</i> (1993) 106:258-268
	AW	Juretic, D. et al., "Conformational Preference Functions for Predicting Helices in Membrane Proteins", <i>Biopolymers</i> (1993) 33:255-273
	AX	Kiyama, R. et al., "Homology Modeling of Gelatinase Catalytic Domains and Docking Simulations of Novel Sulfonamide Inhibitors" <i>Journal of Medicinal Chemistry</i> (1999) 42:1723-1738
	AY	Krautwurst, D. et al., "Identification of Ligands for Olfactory Receptors by Functional Expression of a Receptor Library", <i>Cell</i> (1998) 95:917-926
	AZ	Kuntz, I. et al., "A Geometric Approach to Macromolecule-Ligand Interactions," <i>J. Mol. Biol.</i> (1982) 161:269-288
	AAA	Lim, K. et al., "Molecular Dynamics for Very Large Systems on Massively Parallel Computers: The MPSim Program", <i>J. Comput. Chem.</i> (1997) 18:501-521
	ABB	Malnic, B. et al., "Combinatorial Receptor Codes for Odors", <i>Cell</i> (1999) 96: 713-723
	ACC	Mathiowetz, A.M. et al., "Protein Simulations using Techniques Suitable for Very Large Systems: the Cell Multipole Method for Nonbond Interactions and the Newton-Euler Inverse Mass Operator Method for Internal Coordinate Dynamics", <i>Proteins: Structure, Function, and Genetics</i> (1994) 20:227-247
	ADD	Mayo, S. L. et al. "DREIDING - a generic force field for molecular simulations", <i>J. Phys. Chem.</i> (1990) 94:8897-8909
	AEE	McCammon, J. and Harvey, S.C., <i>Dynamics of Proteins and Nucleic Acids</i> (1987) 51-84
	AFF	McMartin, C. et al., "QXP: Powerful, Rapid Computer Algorithms for Structure-Based Drug Design", (1997) 11:333-344
	AGG	Mombaerts, P., "Seven-Transmembrane Proteins as Odorant and Chemosensory Receptors", <i>Science</i> (1999) 286:707-711
	AHH	Morris, G.M. et al., "Automated Docking Using a Lamarckian Genetic Algorithm and an Empirical Binding Free Energy Function" <i>J. Comp. Chem.</i> (1998) 19(14):1639-1662
	AII	Palczewski, K., et al., "Crystal Structure of Rhodopsin: A G Protein-Coupled Receptor," <i>Science</i> (2000) 289:739-745
	AJJ	Pilpel, Y. et al. "The variable and conserved interfaces of modeled olfactory receptor proteins" <i>Prot. Sci.</i> (1999) 8:969-977
	AKK	Poincelot, R., et al., "Determination of the Chromophoric Binding Site in Native Bovine Rhodopsin," <i>Biochemistry</i> (1970) 9(8):1809-1816
	ALL	Rappé, A.K. et al., "Charge Equilibration for Molecular Dynamics Simulations", <i>J. Phys. Chem.</i> (1991) 95:3358-3363
	AMM	Reshetnikova, L. et al., "Crystal Structures of Phenylalanyl-tRNA Synthetase Complexed with Phenylalanine and a Phenylalanyl-adenylate Analogue", <i>J. Mol. Biol.</i> (1999) 287:555-568

Examiner Signature


Date Considered

9/14/04

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449 (Modified) JUN 04 2004 (37 CFR 1.98(b))		U.S. Department of Commerce Patent and Trademark Office		Attorney's Docket No. 06618-607002	Application No. 10/010,725
Information Disclosure Statement by Applicant (Use several sheets if necessary)				Applicant Wely B. Floriano, Nagarajan Vaidehi, William A. Goddard, III	
				Filing Date November 30, 2001	Group Art Unit 1645 1637
Other Documents (Include Author, Title, Date, and Place of Publication)					
Examiner Initial	Desig. ID	Document			
CDL	ANN	Sachdeva, A. et al., "Nasal Mucociliary Clearance & Mucus pH in patients with Diabetes Mellitus," <u>Indian J. Med. Res.</u> (1993) 98:265-268			
	AOO	Sansom, M. et al., "Modeling Transmembrane Helix Bundles by Restrained MD Simulations", Chapter 14 (pp. 325-347), In Webster, D., <u>Protein Structure Prediction: Methods and Protocols</u> (2000)			
	APP	Schertler, G.F.X., "Structure of rhodopsin", <u>Eye</u> (1998) 12:504-510			
	AQQ	Sharma N., et al., "Efficient introduction of aryl bromide functionality into proteins in vivo", <u>FEBS Lett.</u> (2000) 467:37-40			
	ARR	Shoichet B.K. et al., "Ligand Solvation in Molecular Docking", <u>Proteins: Structure, Function and Genetics</u> (1999) 34:4-16			
	ASS	Schoichet, B.K. et al., "Structure-Based Discovery of Inhibitors of Thymidylate Synthase," <u>Science</u> (1993) 259:1445-1450			
	ATT	Singer, M. et al., "Molecular Modeling of Ligand-Receptor Interactions in the OR5 Olfactory Receptor", (1994) <u>Neuroreport</u> 5:1297-1300			
	AUU	Singer, M.S., "Analysis of the Molecular Basis for Octanal Interactions in the Expressed Rat 17 Olfactory Receptor," <u>Chem. Senses</u> (2000) 25:155-165			
	AVV	Singer, M.S. et al. "Positive Selection Moments Identify Potential Functional Residues in Human Olfactory Receptors", <u>Receptors and Channels</u> (1996) 4:141-147			
	AWW	Tannor, D. et al. "Accurate First Principles Calculation of Molecular Charge Distributions and Solvation Energies from Ab Initio Quantum Mechanics and Continuum Dielectric Theory", <u>J. Am. Chem. Soc.</u> (1994) 116:11875-11882			
	AXX	Uechi et al., "An Automated Structure Prediction System by Lattice Model for Seven-Helix-Type Membrane Proteins", <u>Genome Informatics</u> (1999) 10:239-240			
	AYY	Vaidehi, N. et al., "Prediction of Structure and Function of G Protein-Coupled Receptors", <u>PNAS</u> (2002) 99:12622-12627			
	AZZ	Vaidehi, N. et al. "Constant Temperature Constrained Molecular Dynamics: The Newton-Euler Inverse Mass Operator Method", <u>J. Phys. Chem.</u> (1996) 100:10508-10517			
	AAAA	Vriend, G., "WHAT IF: a molecular modeling and drug design program", <u>J. Mol. Graph.</u> (1990) 8:52-56			
	ABBB	Williams, R.L., et al., "Empirical Solvation Models in the Context of Conformational Energy Searches: Application to Bovine Pancreatic Trypsin Inhibitor," <u>Proteins: Structure, Function, and Genetics</u> (1992) 14:110-119			
	ACCC	Zou, X., et al., "Inclusion of Solvation in Ligand Binding Free Energy Calculations Using the Generalized-Born Model," <u>J. Am. Chem. Soc.</u> (1999) 121:8033-8043			
	ADDD	Floriano, W.B. et al., "Design of Lead Antagonists for Transcriptional Regulation of Glucocorticoid Responsive Elements," U.S. Provisional Application No. 60/233,294, filed 09/15/00			

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Examiner Signature 	Date Considered 9/14/04
EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	

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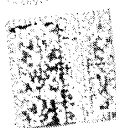
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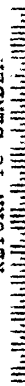
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